REMARKS

Upon entry of the present response, claims 18-20, 33, 43, 48, 66 and 67 are pending in the application. Claim 18 amendments are supported at least, *e.g.*, in the specification at p. 5, lines 14-20, Table 1 and SEQ ID NO:13. In response to the Examiner's request, Applicants provide that previous amendments to claim 18 that recite conserved motif residues, filed in the Response filed 21 April 2003 in the instant application, appear at least, *e.g.*, in the specification at p. 92 lines 3-7. Claim 33 has been amended to more clearly identity the subject matter of the claimed invention, which is disclosed at least, *e.g.*, on page 89, line 11, through page 91, line 9, of the specification. No new matter has been added.

The Office Action.

The outstanding rejections made by the Examiner in the Office Action were the following:

(1) Claims 18-20, 33, 43, 48 and 66-67 were rejected under 35 U.S.C. §101 as not supported by a specific, substantial and credible utility, and under 35 U.S.C. §112, first paragraph, for failing to teach how to use an invention without proper utility;

(2) Claim 18 was rejected under 35 U.S.C. §112, first paragraph, for lack of written description for the FGF family domains and motif;

(3) Claims 66 and 67 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description for a broad class of proteins having post-translational modifications;

(4) Claim 18 was rejected under 35 U.S.C. §112, first paragraph, for lack of written description for a protein having at least 85% homology to SEQ ID NO:2;

(5) Claim 33 was rejected under 35 U.S.C. §112, first paragraph, for lack of written description of an antibody for regulating FGF-CX expression; and

(6) Claim 33 was rejected under 35 U.S.C. §112, second paragraph, for being indefinite.

Applicants are unsure of the scope of the rejection (5) of claim 33, as further elaborated below. Applicants therefore request that the Examiner remove the finality of this Office Action in order to clarify this rejection.

In this Response Applicants further clarify the Patent Office standards that govern these utility rejections (as provided under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph), which Applicants have more than satisfied. A discussion of the patentability of the claims presented is provided below.

35 U.S.C. § 101 Utility Rejection Is Overcome Both On Its Own, And In Combination With The 35 U.S.C. § 112, First Paragraph, Rejection.

Claims 18-20, 33, 43, 48 and 66-67 remain rejected by this Examiner as lacking utility and as being non-enabled. The reason stated is that what is described has no apparent or disclosed specific and substantial credible utility.

Specifically, the Examiner contends that the specification as originally filed did not support a specific utility for the protein recognized by the antibody of the invention because (1) the amino acid sequence identity to other FGF proteins is not sufficient for establishing utility; (2) conservation of FGF family domains does not indicate a conservation of function; (3) the FGF internal hydrophobic domain is merely suggestive that the FGF-CX protein recognized by the antibody of the invention is a new member of the FGF family; (4) the characteristic binding of heparin is not a sufficient utility; and (5)-(6) the biological activity in Examples 9-11 is insufficient to demonstrate an *in vivo* activity, and so is not predictive of administration of the same polypeptide to an animal, and stimulating proliferation of fibroblasts in culture is not a specific utility because the fibroblasts are subsequently transformed in that they lose contact inhibition. See Office Action, section 6, p. 2-4.

The Examiner reiterates the view that homology to FGF family members does not reflect the actual biological function of FGF-CX. The Examiner also reiterates the view that proliferation of NIH 3T3 cells by FGF-CX is not a complete characterization of biological activity, that the loss of contact inhibition in treated cells cannot be separated from the FGF-CX protein's ability to stimulate proliferation, and that Applicants have not shown a proper utility for

a protein that both stimulates and transforms fibroblasts in culture. *Id*, p. 4. The Examiner admits that Applicants have provided multiple utilities for FGF-CX, but alleges that the disclosed uses have no nexus with the biological activity shown in the examples. *Id*, p. 4-6. In addition, the rejections are reiterated that, even though disclosed in a list of uses, the specification as originally filed allegedly did not indicate one specific use intended above all others, such that use in treating the GI tract contradicts use to stimulate new cell growth in neurological disorders, or in treating proliferative disorders including various tumors and benign hyperplasias. *Id*, p. 6, 7. Further, Examiner has dismissed the Jeffers *et al.* reference and the Press Release reporting FDA Approval for treatment of oral mucositis, filed in Applicants' Response to the first Office Action mailed 21 April 2003 ("First Response"), as post-filing evidence of use, alleging that this disclosed use was not substantial at the time of filing because a skilled mechanic in the arts had not physically documented the use. *Id.* Diagnosis and use in cancer is further dismissed because further experimentation would be needed, even though Applicants had disclosed expression of the FGF-CX transcript in both normal and cancer tissues. *Id*, p. 7. Each issue is addressed below.

First, amino acid sequence identity to FGF family members, conservation of family and hydrophobic domains, characteristic binding of heparin, and biological activities shown in Examples 9-17 are more than adequate characterization for one skilled in the art to believe the asserted utility. Applicants again note that utility is properly supported by the structural similarity of this FGF-CX with other known members of the FGF family and specifically contains a conserved family domain, a hydrophobic transport domain and biological activities conserved within the FGF family of proteins. In addition, the FGF-CX encoded by the nucleic acids claimed here has a biological activity similar to a structurally related fibroblast growth factor-9 (FGF-9) compound already known and tested in the art for activation and/or proliferation of glial cells and fibroblasts (which are epithelial cells). *See*, FIGS. 5-9 and specification describing same. Other known FGFs have been demonstrated to be useful in the stimulation of wound healing; see, *e.g.*, U.S. Patent No. 5,804,213. One skilled in the art would find it credible that Applicants' disclosed fibroblast growth factor substantially and specifically

affects the growth of fibroblasts. Applicants' disclosures in Jeffers *et al.*, the Press Release, and the LaRochelle Declaration further support these statements.

In addition, case law holds as valid a utility for claimed compounds based on structural features under facts similar to those in the instant application, *e.g.*, where the Court found utility for claimed compounds having close structural relationship to other compounds known to be useful in cancer therapy in In re Jolles, 628 F.2d 1322 (CCPA 1980); or stated that although it may be true that minor changes in chemical compounds can radically alter their effects, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility in In re Brana 51 F.3d 1560 (Fed. Cir. 1995). Thus, the Examiner must hold this evidence as legally persuasive. There are multiple utilities for the composition of matter being claimed in the application, and they are fully supported and consistent with generally accepted scientific principles as well as in accordance with current case law.

Second, Applicants strongly disagree that a listing containing multiple uses for FGF-CX indicates that none of the uses, including use of FGF-CX for the treatment of ulcers, were substantial at the time the application was filed. *See*, Office Action on page 6. The fact that multiple utilities are recited in the specification does not mean that there is a lack of a specific, substantial and credible utility. As the MPEP makes clear, "[i]t is common and sensible for an applicant to identify several specific utilities for an invention." See MPEP § 2107.01. The case law is also clear. In re Gottlieb 328 F.2d 1016 (CCPA), is particularly relevant. In Gottlieb, multiple utilities were disclosed. The Court held that **one** specific utility was sufficient to meet the utility requirement (328 F.2d at 1018, emphasis added). That is all that is required here also. *See also* In re Brana 51 F.3d 1560 (Fed.Cir. 1995). Applicants once again repeat that their disclosure provides at least one, and in truth multiple, utilities that are substantial, credible and specific.

Applicants have provided unequivocal evidence of record that confirms that the proteins in the instant application have precisely the activities disclosed in the specification. *See* specification, FIGS. 16-19, 22, and 26; as well as Exhibit 1 (Jeffers) and Exhibit 3 (Press Release) in First Response. Jeffers discloses efficacy of FGF-CX in treating ulcerative colitis,

and the Press Release discloses efficacy of FGF-CX in treating oral mucositis, a toxic side effect of chemotherapy and radiotherapy. Both are diseases of the gastrointestinal tract involving fibroblast proliferation. As provided in the specification:

> "The proteins of the invention may be used to stimulate cell growth and cell proliferation in conditions in which such growth would be favorable. An example would be to counteract toxic side effects of chemotherapeutic agents on, for example, hematopoiesis and platelet formation, linings of the gastrointestinal tract, and hair follicles."

See, specification, p. 78, lines 26-29. The specification clearly details stimulation of epithelial cells (including keratinocytes and fibroblasts), glial cells, and cells found in the lining of the gastrointestinal tract. *See, e.g.*, Specification at p. 77, lines 19-30; and p. 78, lines 1-13. Such stimulation can be used to heal wounds and ulcers. *See* Specification at p. 77, lines 29-30. Jeffers and the Press Release merely confirm several of the FGF-CX activities that are recited in the specification. The specification as filed provides all that is needed to prove utility.

Despite admitting to Applicants' multiple disclosures of utility, the Examiner then states that the skilled artisan would need to carry out further research on the claimed invention to determine for which of the possible asserted uses the claimed invention could be used. *See* Office Action p. 7. No experimentation is necessary. Sufficient description is already provided for a person skilled in the art. A skilled artisan is shown that FGF-CX is a growth factor (by its homology to the FGF protein family), and that FGF-CX may be used to stimulate cell growth (by its ability to stimulate growth of NIH 3T3 fibroblasts). *See* above. In addition, the skilled artisan is given corroborative proof that confirms the disclosure that FGF-CX can and does stimulate GI cell proliferation and treat oral mucosis. *See* Jeffers *et al.* and Press Release from the First Response. A skilled artisan can make no other valid conclusion except that FGF-CX can and does substantially and specifically stimulate epithelial cells, including at least those fibroblast of the GI tract.

Third, the claims being prosecuted are to antibodies to the FGF-CX protein compositions. They are not to methods of treating the GI tract or cancer. That is but one of the listed utilities of the claimed invention. As stated in Gottlieb, one specific utility is sufficient to meet the utility requirement. *See*, 328 F.2d at 1018. The GI tract has epithelial cells, but so does any other

tissue in the body that contains fibroblast. *See, e.g.*, specification, p. 6, lines 3-7. Any one of these supports the multiple credible, substantial and specific uses already disclosed in the specification. We state once again that the proper standard of review under Gottlieb is that one and only one disclosed utility is needed to meet the requirements of 35 U.S.C. §§101, 112. *See*, 328 F.2d at 1018. Applicants have submitted unequivocal evidence of record that confirms that the FGF-CX proteins encoded by the claimed nucleic acids have these activities at the very least.

Applicants have provided the Examiner with the Jeffers *et al.* reference and the Press Release in Applicants' First Response filed 21 April 2003. As shown above, the specification clearly discloses utility of the proteins of this invention for treating ulcers and cells lining the gastrointestinal tract in accordance with the requirement of the patent statutes. As illustrated in the Jeffers article (Exhibit 1 in First Response), the proteins of this invention have a demonstrated therapeutic activity of treating intestinal inflammation in both animal *in vivo* studies and *in vitro* studies using human cell lines. In the scientifically acceptable murine-colitis model, it was shown that prophylactic administration of FGF-CX (corresponding to SEQ ID NO:2 of the claims before the Board) significantly reduced the severity and extent of mucosal damage; in the scientifically accepted rat small bowel ulceration/inflammation model, administration of FGF-CX was shown to reduce small intestinal weight gain, necrosis, inflammation, and weight loss; and in *in vitro* studies it was demonstrated that FGF-CX stimulated cell growth and restitution in human intestinal fibroblast cell lines. Accordingly, FGF-CX (SEQ ID NO:2) has been shown to have a specific, substantial, and credible utility of treating intestinal disorders. This utility was specifically disclosed in the specification as originally filed.

Fourth, evidence of FGF-CX *in vivo* activity is not required to proved utility, in contrast to statements by the Examiner. The only requirement is for a disclosure of a real world activity is, not proof of an FDA approved use. However, *in vivo* data is provided at least, *e.g.*, in FIGS. 15A, 15C, 15D, 18, 19, and Examples 8 and 11, which disclose both FGF-CX expression in normal human tissue and its effect on transformed cells implanted in nude mice.

A causal relation is shown in Examples 9-17 between expression of FGF-CX and proliferation of treated fibroblast cells as compared to non-treated fibroblast cells. Applicants agree with the Examiner that transformed cells in culture do not represent an *in vivo* model of FGF-CX protein activity in an animal. Instead, these experiments are clear evidence that FGF-CX is a growth factor for these fibroblast cells. They are also clear evidence that over-expression of FGF-CX polypeptide is sufficient for transformation, which corroborates Applicants' assertion that the claimed antibodies against FGF-CX have utility in treating cancers associated with over-expression of FGF-CX. *See*, at least specification at *e.g.*, pp 17-18, 67-68, 77 and FIG. 15.

Finally, the Examiner reiterates the "how to use" utility-based § 112, first paragraph, rejection, but did not provide any legally proper reasons for doing so. For an Examiner to uphold a utility-based §112, first paragraph, rejection, a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result." Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555 (Fed. Cir. 1992), as discussed in the Legal Analysis accompanying the Utility Guidelines (M.P.E.P. § 2107). The only instances in which the Federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention *could and did not work* as the inventor claimed it did." M.P.E.P. § 2107 (emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.01. That is simply not the case here, because (a) Applicants disclose the use of the invention as a growth factor, *e.g.*, at least on cells of the GI tract; and (b) the utilities provided in the specification do not violate scientific principle. In fact, they are upheld, *e.g.*, at least in the Jeffers paper and the Press Release on the FDA's approval of the IND. *See*, Exhibits 1 and 3 from First Response.

The rejections should be withdrawn.

35 U.S.C. § 112, first paragraph, rejection is overcome.

Claim 18 was rejected under 35 U.S.C. §112, first paragraph, for lack of written description for the conserved FGF family domains and motif. Applicants apologize for not specifically stating the full range of support for the last amendments to claim 18. Applicants have amended the claim in part, and in part now recite the proper location for support.

Applicants have amended claim 18 to provide that the hydrophobic transport domain resides between residues 90-115, as shown in Table 1 and SEQ ID NO:13. However, support is provided in the specification for the conserved motif at residues at 125, 127, 129, 136, 137, 141 and 148 as provided in the currently pending amended claim 18. The double underlined sequence in FIG. 13 discloses the FGF signature motif, as described in the specification at page 92, lines 3-7, wherein:

> An FGF signature motif, G-X-[LI]-X-[STAGP]-X(6,7)-[DE]-C-X-[FLM]-X-E-X(6)-Y, identified by a PROSITE search (Bucher, P. & Bairoch, A. (1994) *Ismb.* 2, 53-61) located between amino acid residues 125-148 is double-underlined, and intron/exon boundaries are depicted with arrows.

Applicants assert that the claim as amended makes the rejection moot, and request that it be withdrawn.

Claims 66 and 67 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description for a broad class of proteins having post-translational modifications other than proteolytic cleavage, and specifically phosphorylation or N-myristoylation. Applicants traverse. Page 12, lines 14-19 provide as follows:

> Further as used herein, a "mature" form of an FGF-CX polypeptide or protein may arise from a step of post-translational modification other than a proteolytic cleavage event. Such additional processes include, by way of non-limiting example, glycosylation, myristoylation or phosphorylation. In general, a mature polypeptide or protein may result from the operation of only one of these processes, or a combination of any of them.

This claim language is taken word for word from the disclosure, thus it is fully supported by the written description. This rejection should be withdrawn.

Claim 18 was rejected under 35 U.S.C. §112, first paragraph, for lack of written description for a protein having at least 85% homology to SEQ ID NO:2. Applicants have amended claim 18 to provide that homology should be at least 95% identity to SEQ ID NO:2. Determination of identity (which is equivalent to homology) is defined at least, *e.g.*, on p. 37, lines 7-14, of the specification. The claim limitation remains that the amino acid substitutions be made according to Table 2. Hence, the variant polypeptides are fully taught in the specification, and guidance is provided to those skilled in the art. This rejection should be withdrawn.

Claim 33 was rejected under 35 U.S.C. §112, first paragraph, for lack of written description for "an antibody that is capable of regulating the FGF-CX expression." Applicants traverse in that the claim language has been mis-characterized. Claim 33 recites an antibody that "alters the functional growth factor-like properties of the polypeptide." A protein's expression and functional properties are not synonymous. One skilled in the art would refer to transcriptional expression and contrast this with post-translational functional properties. Therefore, Applicants are unsure what is being rejected by the Examiner.

Applicants therefore request that the Examiner remove the finality of this Office Action in order to clarify this rejection.

The Examiner further states that claim 33 is unclear as to the pathology Applicants intend to treat. As noted below, Applicants have amended claim 33 to indicate that the pathology "comprises" aberrant expression, aberrant processing, or aberrant physiological interactions of the polypeptide of claim 18, thus defining the pathology. The "Methods of Treatment" section in the specification on pages 89-91 characterizes these pathologies.

The rejections should be withdrawn.

The 35 U.S.C. § 112, Second Paragraph Rejections Are Overcome.

Claim 33 was rejected under 35 U.S.C. §112, second paragraph, for being indefinite for reciting the phrase "treatment of a pathology and functional growth factor like properties" where it is allegedly unclear what pathology is treated or what growth factor-like properties are altered by the antibody of the claimed invention.

Claim 33 has been amended to indicate that the pathology "comprises" aberrant expression, aberrant processing, or aberrant physiological interactions of the polypeptide of claim 18, thus defining the pathology. Support appears in the specification at least, *e.g.*, on page 89, line 11, through page 91, line 9.

Upon entry of the amendments, these rejections are moot and should be withdrawn.

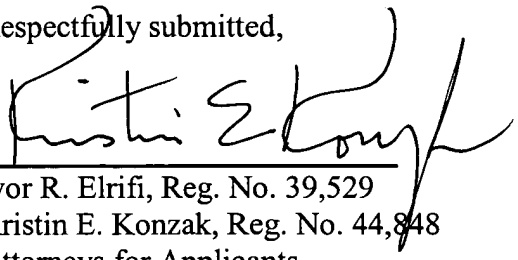
CONCLUSION

Applicants submit that the application is in condition for allowance, and such action is respectfully requested. Applicants request that the finality of the current Office Action be withdrawn in order to clarify the current rejections. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

A petition requesting a one month extension of time and check #17763 for $55.00 to cover the extension fee due under 37 C.F.R. 1.17(a)(1) are enclosed. With the petition, this filing is timely when filed on Monday, December 22, 2003.

No additional fee is believed due at this time. The Commissioner is hereby authorized to charge payment of any filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 15966-557 CIP2).

Respectfully submitted,



Dated: December 22, 2003

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